LINKER, ANTIBODY-DRUG CONJUGATE INCLUDING SAME AND USE THEREOF

[0001] The present application is based on and claims the benefit of priority from Chinese application No. 201810939770.0, filed on Aug. 17, 2018, the disclosures of which are incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present application belongs to the field of medicinal chemistry, specifically relates to a linker, a linker-containing antibody-drug conjugate and use of the linker, as well as a pharmaceutical composition comprising the antibody-conjugated drug and use of the antibody-drug conjugate for treating and/or preventing a disease.

BACKGROUND ART

[0003] Tumors are still the main cause of human deaths due to diseases. The continuous emergence of new therapies is bringing revolutionary changes to cancer treatment. In recent years, CAR-T cell therapy and PD-1/PD-L1 antibody immunotherapy have made breakthrough progress, however, the indications of CAR-T cell therapy are limited to hematological malignancies, and the objective response rate of PD-1/PD-L1 antibody immunotherapy is only 20% to 30%. For most malignant tumors, the treatment methods are still limited and it is still necessary to expand existing therapies and create synergy by continuous innovation.

[0004] In recent years, the strategy for malignant tumor treatment is gradually shifting from traditional chemotherapies to antibody-based targeted therapies. However, in general, traditional treatment methods are still the first choice in clinical practice and chemotherapeutic drugs still occupy the largest share of the cancer treatment market in terms of product numbers. Due to their poor targeting and biodistribution, small-molecule chemotherapeutic drugs are prone to generate serious toxic and side effects, resulting in poor patient compliance and difficulty in obtaining satisfactory clinical benefits. Compared with chemotherapeutic drugs, monoclonal antibody drugs have better targeting and pharmacokinetic properties and have played an increasingly important role in the treatment of malignant tumors, however, they also have deficiencies such as poor tissue penetration, weak biological activity and easiness to produce resistance.

[0005] In the context of a serious lack of overall high-quality targets for new drug development, the emergence of antibody-drug conjugates (ADCs) has achieved a strong combination of advantages of small molecule chemotherapeutic drug and antibody and it has become one of the most promising directions besides tumor immunotherapy. The structure of antibody-drug conjugate comprises three parts: an antibody, a small molecule cytotoxin and a linker that realizes the organic combination of the former two parts. By means of the targeting property of antibody, cytotoxin of ADC is accumulated on a tumor target site to achieve the effects of increased efficacy and reduced toxicity and the released cytotoxin can further kill surrounding tumor cells through the bystander effect. The IC_{50} of cytotoxin is usually 10^{-10} to 10^{-12} mol/L and the common cytotoxins are tubulin inhibitors MMAE and DM1. Compared with conventional chemotherapeutic drug, ADC shows a significantly improved therapeutic index.

[0006] In addition to the targeted drug delivery based on antibody, another major advantage of ADC is that the secondary drug resistance caused by monoclonal antibody may be overcome to a certain extent, because the efficacy of ADC mainly depends on cytotoxin rather than antibody, and its targeted binding would not be affected by a certain degree of tumor mutation. For example, ADC drug Kadcyla, which is composed of monoclonal antibody Herceptin and cytotoxin DM1, can still effectively treat $HER2^+$ breast cancer after Herceptin resistance and can substantially prolong the overall survival (OS) by nearly 6 months in comparison with the standard therapy of capecitabine/lapatinib. In addition, the clinical phase III evidence-based medicine studies with code names of MARIANNE, KAMILLA, etc. have confirmed that Kadcyla single drug showed an efficacy not inferior to that of the standard therapies and had better safety. This drug has now been included in the breast cancer guidelines as a first-line alternative anti-HER2 regimen. ADCs are characterized by high activity, low toxic and side effects and long duration of action, and the emergence of such drugs provides a new strategy for the "precision treatment" of tumors.

[0007] In biological macromolecules such as antibodies, heavy and light chains are often linked by disulfide bonds at defined positions. The free sulfhydryl groups generated by selective reduction of disulfide bonds between light and heavy chains of antibody molecules have been widely used as antibody modification sites to obtain ADC drugs in which antibody cysteine residues are used as coupling sites, the first successful marketed ADC drug Brentuximab Vedotin (Adcetris) adopts this coupling method. In addition, the emerging sulfhydryl site-directed mutagenesis engineered antibody (THIOMAB) has an improved uniformity of ADC drug to a certain extent and the coupling site of this type of antibody is also sulfhydryl coupling site. In the preparation process of the above-mentioned various types of ADC, thiosuccinimide may be generated by Michael addition reaction between a free sulfhydryl group in the antibody structure and a maleimide group to realize the small molecule drug modification process of antibody (FIG. **1**) and this addition reaction has now become an indispensable tool in the preparation process of ADCs currently on the market and in clinical research.

[0008] The structure of thiosuccinimide is widely used in ADC linkers. At present, the two mainstream ADC drugs Adcetris® and Kadcyla® and a large number of clinically researched ADCs all contain thiosuccinimide structural fragments. The wide application of thiosuccinimide structure in biological coupling is mainly based on two points: (1) the structure can be directly obtained through the Michael addition reaction between maleimide structure and sulfhydryl group under mild biological conditions; (2) the addition reaction has high selectivity and good reaction kinetic properties and the coupling process can be quantitatively completed in a very short time without a large excess of substrate.